

# EHA-MSH Hematology Tutorial

Self-assessment Case Session 3:  
Treatment of Newly Diagnosed Hodgkin  
Lymphoma

*Speaker: Anna Czyz*

Kuala Lumpur, Malaysia  
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# | Disclosures

## Takeda

- Presenter has received lecture fees, honorarium as an advisory board member, travel grants

## BMS

- Presenter has received lecture fees, travel grants

# | Case presentation

## Patient profile

- 34-year-old female patient
- Occupation: Teacher
- Not pregnant

# | Case presentation

## Main complaints

- Patient presented with noticeable swelling of lymph nodes in the neck and a persistent cough
- Enlargement of cervical lymph nodes on palpation; patient noted that the cough had been bothering her for several weeks
- Patient reported occasional night sweats and a feeling of fatigue

## Medical history

- No relevant medical history
- No reported family history of hematological conditions, including lymphoma

# | Diagnostic workup

## Clinical presentation

- Patient appeared generally fatigued but otherwise in good health
- Patient expressed concern about the persistent swelling of lymph nodes in her neck and the associated cough
- No other significant symptoms reported

## Physical examination

- A thorough physical examination revealed palpable lymphadenopathy in the cervical region
- The rest of the examination was otherwise within normal limits

# | Diagnostic workup

## Imaging studies

- Initial chest and abdomen CT showed:
  - Enlarged lymph nodes in the lower neck
  - Extensive prominent heterogenous lymph nodes in the mediastinum with extensive infiltrative changes in the lungs
    - Greatest extent of changes in the left-lower lobe
    - Up to 134 × 85 mm in the transverse plane
  - Presence of fluid in the left-pleural cavity and pericardial sac
  - Enlarged retroperitoneal lymph nodes in the abdominal cavity, partially merging into bundles

# | Diagnostic workup

## **Excisional biopsy of enlarged lymph nodes in the lower neck**

- Histopathological examination of the biopsy specimen revealed characteristic features consistent with classical Hodgkin lymphoma
- Further characterization of Hodgkin lymphoma subtype was performed based on additional immunohistochemical markers and histological features
  - PAX5 dim, CD30<sup>+</sup>, CD15<sup>-</sup>, CD20<sup>-</sup>, MUM1<sup>+</sup>
- Tumor was classified as being of mixed-cellularity subtype

# | Summary of the initial PET/CT scan results

## Head and neck

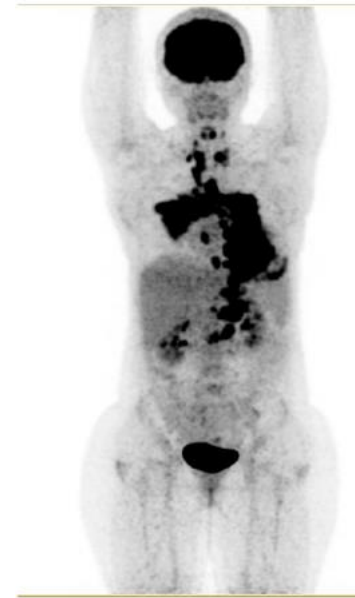
- Enlarged active metabolic in the lower neck bilaterally with increased FDG uptake ( $SUV_{max}$  7.4)

## Chest

- Active metabolic hilar lymph nodes merge with infiltrative changes in the lungs: not measurable ( $SUV_{max}$  8.4)
- Extensive infiltrative changes in the lungs with the greatest extent of changes in the left-lower lobe ( $SUV_{max}$  8.9)
- Fluid in the left-pleural cavity (up to 15 mm), and pericardial sac (up to 18 mm)

## Abdomen and pelvis

- Enlarged active metabolic retroperitoneal lymph nodes in the abdominal cavity ( $SUV_{max}$  7.6)



**PET/CT scan before treatment**



# | Question 1: What clinical stage should be diagnosed according to the Lugano classification?

1. Stage IIIBE
2. Stage IIIB
3. Stage IVBE
4. Stage IVB
5. Clinical stage can not be determined without bone-marrow biopsy

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# Clinical stages according to the Lugano classification

**Table 2.** Revised Staging System for Primary Nodal Lymphomas

Stage	Involvement	Extranodal (E) Status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky*	II as above with “bulky” disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

NOTE. Extent of disease is determined by positron emission tomography-computed tomography for avid lymphomas and computed tomography for nonavid histologies. Tonsils, Waldeyer’s ring, and spleen are considered nodal tissue.  
 \*Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

**If PET/CT is performed, a bone marrow aspirate/biopsy is no longer required for the routine evaluation of patients with Hodgkin lymphoma**

# | Diagnostic workup

## Laboratory investigations

- CBC with WBC differentiation
  - WBC:  $10.5 \times 10^9/L$
  - ANC:  $8.5 \times 10^9/L$
  - ALC:  $0.9 \times 10^9/L$
  - AMC:  $0.5 \times 10^9/L$
  - Hb: 108 g/L
  - Platelets:  $420 \times 10^9/L$
- Metabolic panel
  - Albumin: 40 g/L
  - LDH: 380 IU/L (UNL: 222 IU/L)
  - No abnormalities in the other tests
- ESR: 60 mm/hour

## Question 2: What is the International Prognostic Score (IPS) in this patient?

1. IPS of 1
2. IPS of 2
3. IPS of 3
4. IPS of 4
5. IPS of 5

### 34-year-old female patient; clinical stage IVB

- WBC:  $10.5 \times 10^9/L$
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# Diagnostic workup: IPS calculation

- Serum Albumin <4 g/dL (1 point)
- Hemoglobin <10.5 g/dL (1 point)
- Male Sex (1 point)
- Stage IV Disease by Ann Arbor Classification (1 point)
- Age  $\geq$ 45 Years (1 point)
- White Cell Count  $\geq$ 15,000/mm<sup>3</sup> (1 point)
- Lymphocyte Count <600/mm<sup>3</sup> or <8% of White Cell Count (1 point)

**IPS: 1**

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# Question 3: What options for first-line treatment can be used outside of clinical trials?

1. ABVD with an interim PET/CT response after 2 cycles to guide further treatment
2. ABVD with EOT-PET/CT after 6 cycles
3. A-AVD with an interim PET/CT after 2 cycles to guide further treatment
4. A-AVD with an EOT-PET/CT after 6 cycles
5. Escalated BEACOPP with an interim PET/CT after 2 cycles to guide further treatment
6. BrECADD with interim PET/CT after 2 cycles to guide further treatment

**Indicate correct answers:**

**A. 1, 3, 5**

**B. 1, 3, 6**

**C. 2, 4, 5**

**D. 1, 4, 6**

**E. 1, 3, 5**



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## Indicate correct answers:

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- B. 1, 3, 6
- C. 2, 4, 5
- **D. 1, 4, 6**
- E. 1, 3, 5

# | Optimal first-line treatment: Summary

## ABVD with an interim PET/CT response after 2 cycles to guide further treatment

- After two ABVD cycles, nearly one-fifth of patients with advanced-stage classical Hodgkin lymphoma have a positive interim PET and may benefit from intensified treatment<sup>1-3</sup>

# | Optimal first-line treatment: Summary

## A-AVD with an EOT response evaluation by PET/CT after 6 cycles

- The prognostic/predictive value of interim PET on treatment outcome was not included in the prespecified prognostic group analysis of the ECHELON-1 trial,<sup>1</sup> but was evaluated in the 5-year follow-up analysis<sup>2</sup>
  - Continuing BV-AVD after a positive interim PET is an acceptable strategy based on the 60.6% PFS rate at 5 years
- The COBRA (EORTC-1537) phase 2 study exploring the significance of early metabolic response after 1 cycle of BV-AVD revealed a high rate of false positive results for interim PET after a single course of BV-AVD and high response rate already after 1 cycle of BV-AVD, as measured by FDG-PET and serum TARC level<sup>3</sup>

# | Optimal first-line treatment: Summary

## BrECADD with interim response evaluation by PET/CT after 2 cycles

- In the GHSB HD21 international open-label phase 3 trial, adult patients age  $\leq 60$  years with advanced-stage classical Hodgkin lymphoma were randomized in a 1:1 ratio to 4–6 PET-2-guided cycles of either eBEACOPP or BrECADD<sup>1</sup>
- Trial establishes non-inferiority of BrECADD vs eBEACOPP
  - 3-year PFS: 94.9% vs 92.3%<sup>2,3</sup>
- Treatment-related morbidities are significantly reduced with BrECADD vs eBEACOPP<sup>4,5</sup>

## Question 4: Reduction in which treatment-related morbidities have been demonstrated in the GHSB HDS21 study for BrECADD vs eBEACOPP ?

1. Lung toxicity, secondary neoplasms
2. Infections, lung toxicity
3. Infections, lung toxicity, liver toxicity
4. Bone destruction, weight gain, cardiovascular toxicity
5. Hematological toxicity, transfusion frequency, peripheral neuropathy, gonadal toxicity

## Question 4: Reduction in which treatment-related morbidities have been demonstrated in the GHSG HDS21 study for BrECADD vs eBEACOPP ?

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5. **Hematological toxicity, transfusion frequency, peripheral neuropathy, gonadal toxicity**

# | GHSB HD21: Treatment-related morbidity with BrECADD vs eBEACOPP<sup>1-3</sup>

- Reduction in treatment-related morbidity was clinically meaningful, with a relevant reduction of:
  - Transfusion frequency for red blood cells: 24% vs 53%
  - Transfusion frequency for platelets: 17% vs 34%
  - Peripheral neuropathy (sensory): 38% vs 49%
  - FSH levels within the normal range indicating normal gonadal function
    - Mean FSH value in young female patients: 13.4 U/L vs 27.2U/L

# | First-line treatment: Case report

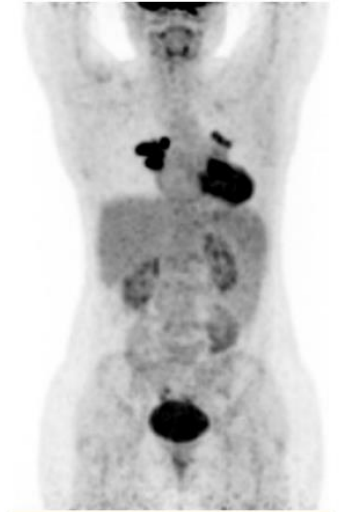
- Patient was initially treated with 2 cycles of ABVD
- After 2 cycles of ABVD, PET/CT was performed



# Summary of the interim PET/CT scans results

## Chest

- Active metabolic infiltrative changes are still present in the upper lung lobes
- The extent of changes is smaller, but metabolic activity remains high
  - On the right side:  $\sim 52 \times 44$  mm ( $SUV_{max}$  8.2)
  - On the left side:  $\sim 50 \times 35$  mm ( $SUV_{max}$  8.7):
  - In the left-lower lobe, infiltrative nonobstructive changes with air bronchograms and diffuse increased FDG uptake ( $SUV_{max}$  1.7); most likely an inflammatory component
- Fluid in the left-pleural cavity (up to 19 mm)



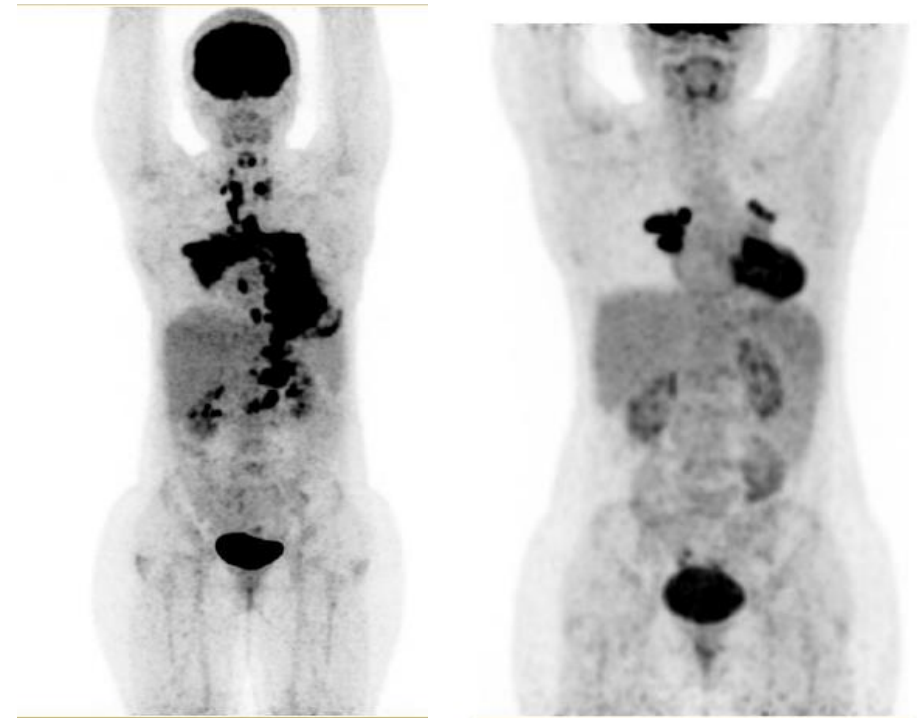
**PET/CT scan after the second cycle of ABVD (interim PET)**

## Conclusions

- PET/CT results indicate a partial metabolic response to the treatment
- Significant regression of nodal morphological and metabolic changes on both sides of the diaphragm
- Active metabolically infiltrative changes persist in the lungs without significant changes
  - Deauville score 5

# Question 5: What is the optimal treatment based on the interim PET/CT scan results?

1. Continuation of treatment up to 6 cycles of ABVD followed by localized radiotherapy to PET-2 positive sites
2. De-escalation of treatment  
→ administration of 4 cycles of AVD
3. Administration of 4 cycles of AVD treatment with brentuximab vedotin (A-AVD)
4. Escalation of treatment  
→ administration of 4 cycles of escalated BEACOPP
5. Switch to salvage treatment for refractory Hodgkin lymphoma → optimal chemotherapy in combination with a PD-1 inhibitor



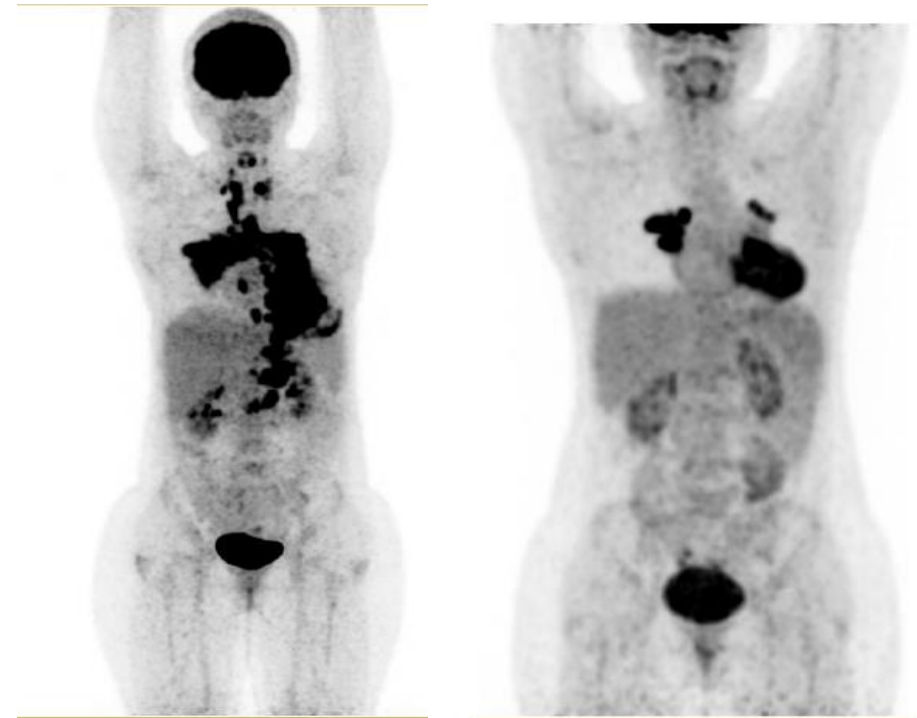
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PMR

Deauville score of 5

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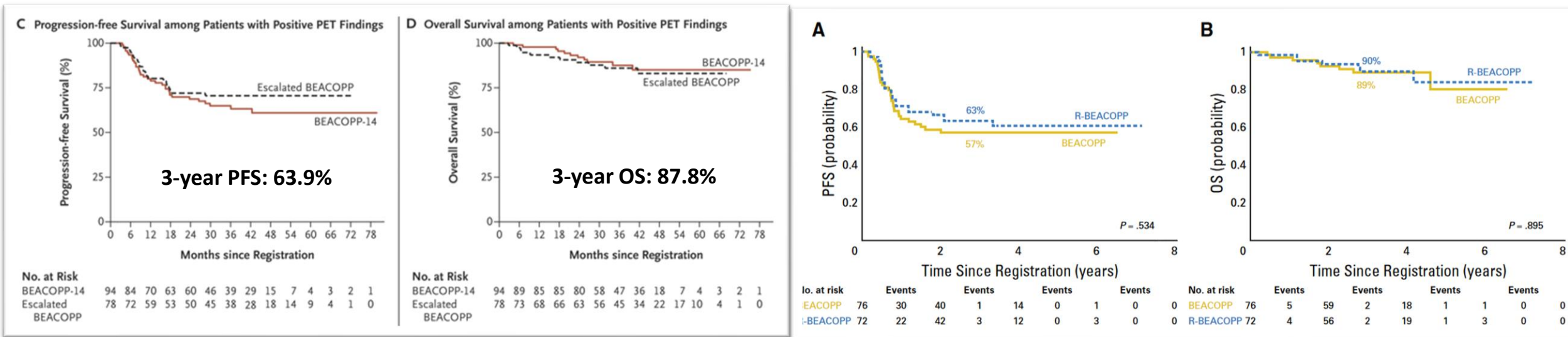


**PET/CT scan after the second cycle of ABVD (interim PET)**

PMR

Deauville score of 5

# Trials evaluating therapy escalation in interim PET-positive patients after 2 cycles of ABVD

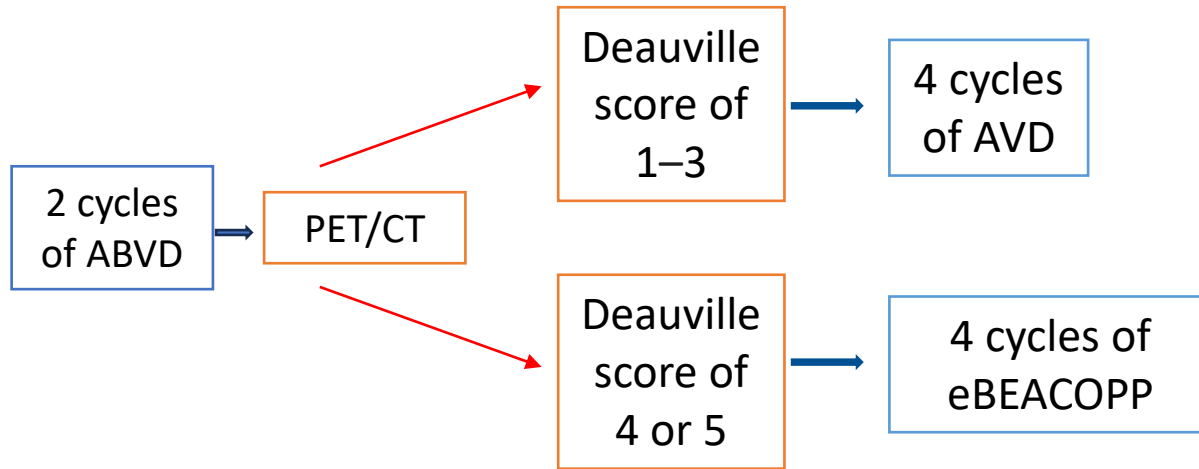


RATHL study<sup>1</sup>

GITIL/FIL HD 0607 Trial<sup>2</sup>

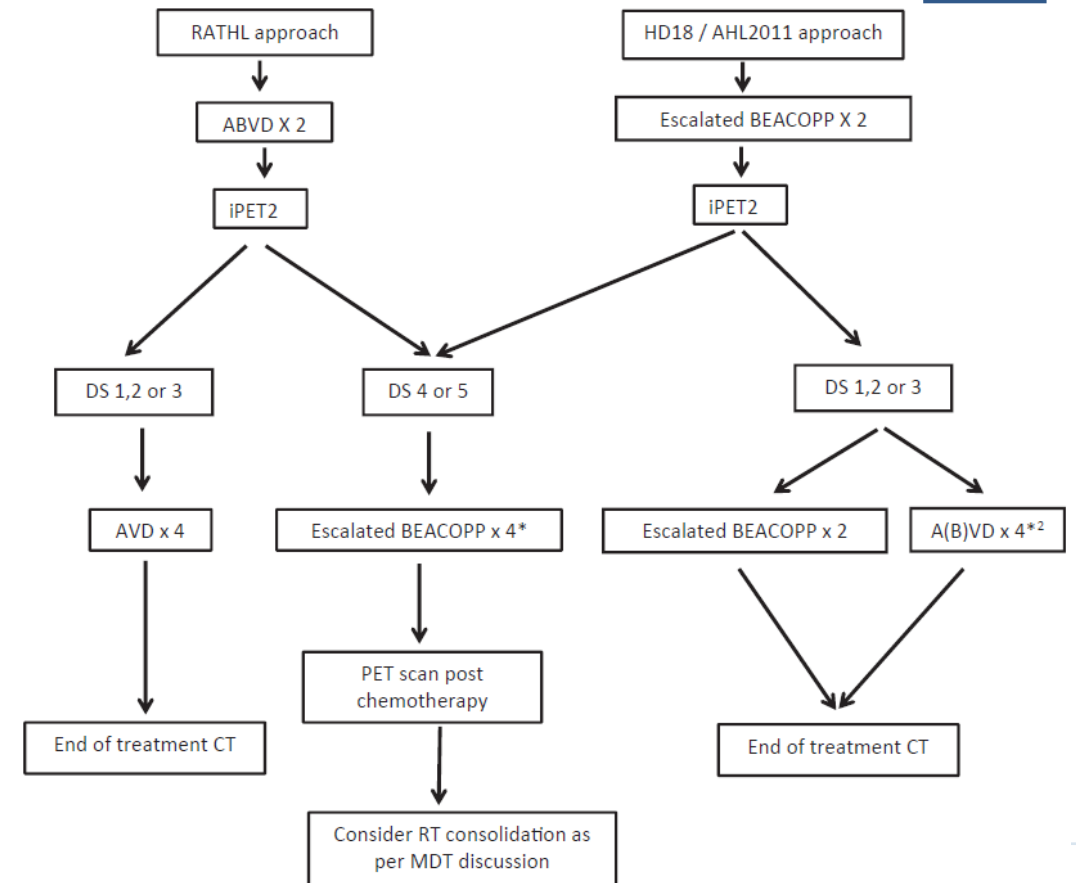
# Recommendation for patients with PET-2-positive advanced classical Hodgkin lymphoma treated with 2 cycles ABVD

NCCN Guidelines Version 3.2024  
Hodgkin lymphoma (age 18–60 years)<sup>1</sup>



British Society for Haematology guidelines<sup>2</sup>

FOLLOWS ET AL.



# | Case report: Treatment

- Patient received 4 cycles of eBEACOPP

# | Question 6: When should EOT-PET/CT be performed?

1. Immediately following completion of chemotherapy
2. Two weeks post chemotherapy
3. 3 to 6 weeks post chemotherapy
4. Three months post chemotherapy
5. Six months post chemotherapy

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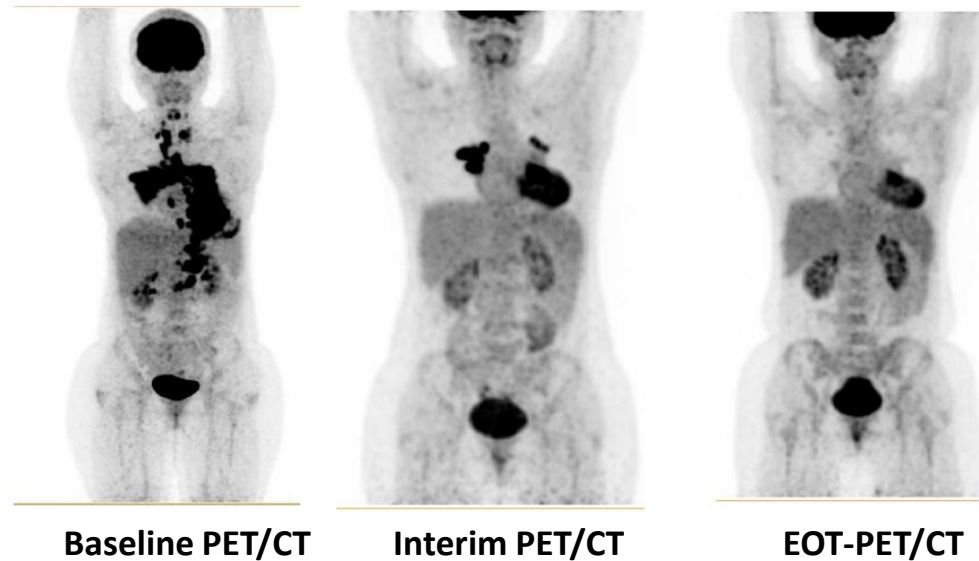


# | EOT-PECT/CT assessment

- PET should be planned for 3 to 6 weeks post chemotherapy or 3 months post radiotherapy, if no clinical concerns for progressive disease

# Treatment continuation: Case report

- Patient received 4 cycles of eBEACOPP
- EOT-PET/CT was performed 6 weeks after the completion of treatment
- The conclusions of the EOT-PET/CT scans:
  - PET/CT showed partial morphological and significant metabolic regression of the lesions
  - Only residual infiltrative lesions in the right lung show mediocre metabolic activity (FDG uptake above uptake in MBPS, below uptake in the liver); Deauville score 3



# | Case report: Monitoring the patient

- The patient is monitored on an outpatient basis and is living in complete metabolic remission 18 months after completion of chemotherapy
- Involved-site radiation therapy was omitted
- PET/CT was repeated after 6 months due to risk factors for early relapse:
  - Interim PET/CT positive
  - EOT-PET/CT: Deauville score of 3
  - Primary involvement of extranodal sites (lungs)
- Complete metabolic response was confirmed by PET/CT
  - Deauville score of 2

# References

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